

"fibrogen" with "fibrinogen," which corrects a typographic error. No new matter is added.

III. Objection to the specification

The specification has been amended to add headings and an abstract on a separate page. Applicants respectfully request that the objection be withdrawn.

IV. Claim rejections

A. 35 USC §112 Second Paragraph

Claims 29, 30, 33, 36-42, 51, and 54-60 were rejected under 35 USC §112 second paragraph as allegedly being indefinite. In particular, the Examiner objected to the phrase "based on" in claim 29. The present amendment has replaced "based on" with "comprising," according to the Examiner's suggestion. The Examiner further objected to the ratios in claims 36 for lack of clarity. The present amendment addresses these issues. Applicants thus submit the rejections under 35 USC §112 second paragraph should be properly withdrawn.

B. 35 USC §103(a)

The Examiner rejected claims 29, 30, 33, 36-42, 51, 54-60, and 70-73 under 35 USC §103(a) as allegedly being obvious over U.S. Patent No. 5,418,221 (Hammarstrom) or U.S. Patent No. 5,631,011 (Wadstrom) in view of U.S. Patent No. 5,271,939 (Robertson) or WO 92/22309 (WO) and further in view of U.S. Patent No. (Atkinson). Applicants respectfully traverse the rejections.

The Examiner stated that Hammarstrom and Wadstrom both disclose tissue adhesives containing fibrinogen and plasminogen, which are used for wound healing; Robertson and WO teach the use of elastase inhibitors in surgery and wound healing; Atkinson discloses eglin as an elastase inhibitor. Thus, the Examiner took the position that it would have been obvious to use an elastase inhibitor, such as eglin, in the fibrinogen-based tissue adhesives because the references relate to surgery and/or wound healing and are for the same purpose. Last paragraph on page 5 of the Office Action.

Applicants do not agree with the Examiner's characterization of the references, particularly Robertson and WO. Hammarstrom discloses a tissue adhesive used for joining living mineralized tissue, such as teeth or bones, or facilitating introduction of artificial implants, such as tooth implants and artificial joints. Some embodiments of Hammarstrom's adhesive contain fibrinogen, Factor XIII, thrombin, and, optionally, aprotinin. Wadstrom teaches a tissue adhesive comprising fibrin or fibrinogen and a polymer for a desirable viscosity and reduced scar formation during wound healing. Robertson relates to methods and compositions useful for preventing and treating corneal haze caused by exposure to laser irradiation during eye surgery. Various so-called "wound healing modulators" are used according to Robertson, which also suggests the use of elastase inhibitors as "epithelial cell health promoters" that contribute to the overall health of the eye. WO describes therapeutic agents comprising 4-(4-chlorophenyl-sulphonylcarbamoyl)benzoyl-L-valyl-L-proline 1(RS)-(1-trifluoroacetyl-2-methylpropyl)amide, an elastase inhibitor, for the treatment and prevention of certain vascular diseases and conditions (such as myocardial ischemia and stroke) in which neutrophils are involved or implicated. Atkinson discloses eglin as an inhibitor of elastase.

To establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the claims limitations. MPEP§2143. See also *In re Rouffet*, 47 USPQ2d 1453. The court in Rouffet stated that "even when the level of skill in the art is high, the Board must identify specifically the principle, known to one of ordinary skill, that suggests the claimed combination."

Rouffet at 1459.

The elements of the pending claims, *e.g.*, a fibrinogen-comprising tissue adhesive and use of an elastase inhibitor, are separately disclosed in the above-cited

references. Yet, the references do not provide any suggestion or motivation to one of skill in the art to combine the elements. The Examiner asserted that the use of fibrinogen in the tissue adhesives of Hammarstrom and Wadstrom is for the same purpose as the use of an elastase inhibitor in the compositions of Robertson and WO, and that one of skill in the art would thus be motivated to combine the ingredients for enhanced effects of the resulting composition. Applicants cannot agree. The use of fibrinogen by Hammarstrom or Wadstrom may be for purposes generally related to the present invention, e.g., in a tissue adhesive for rejoining living tissue. As the Examiner has conceded, neither Hammarstrom nor Wadstrom has suggested adding an elastase inhibitor in their respective compositions. The use of an elastase inhibitor by Robertson, however, relates to treatment and prevention of corneal haze. Although the exact mechanism of corneal haze was not fully understood, several possibilities were offered (see, e.g., column 4 lines 28-40). Elastase inhibitors were used as compounds known to contribute to the health of epithelial cells of the corneal (column 11 lines 37-44 and column 12 lines 3-15) and not for their effect of preventing fibrinolysis. Thus, Robertson's teaching of using elastase inhibitors would not suggest or motivate one of skill in the art of developing tissue adhesives to add an elastase inhibitor as an additional ingredient in a tissue adhesive composition.

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The use of elastase inhibitors in WO is also significantly different from the general purpose of using fibrinogen in a tissue adhesive. Fibrinogen is an essential component in a tissue adhesive, e.g., the tissue adhesive disclosed by Wadstrom, for the process of thrombosis that rejoins tissue of a wound or at the site of a surgery. In this situation, premature fibrinolysis is undesirable and sought to be prevented, which is precisely why elastase inhibitors are used in the tissue adhesives of the present invention (see, e.g., page 6 lines 3-12). On the other hand, WO relates to treatment of vascular diseases where dissolution of blood clots is desirable and in fact teaches the use of thrombolytic agents (see, e.g., page 4 the first and second full paragraph). The use of the elastase inhibitor, 4-(4-chlorophenyl-sulphonylcarbamoyl)benzoyl-L-valyl-L-proline

1(RS)-(1-trifluoroacetyl-2-methylpropyl)amide, is thus not connected by WO to its property to prevent fibrinolysis. One skilled in the art would therefore not be suggested or motivated to add an elastase inhibitor into his tissue adhesive upon learning the invention disclosed by WO.

Moreover, there is no reasonable expectation of success for one to obtain a tissue adhesive with the desired properties in combining the elements. As discussed above, Robertson teaches the use of elastase inhibitors to generally promote the overall health of the corneal in the context of treating and preventing corneal haze; WO teaches the use of a particular elastase inhibitor for treating vascular diseases, where fibrinolysis is desired rather than to be prevented (at least for a period of time) as in the present invention. Hence, it cannot be fairly said that, in light of the disclosure of Hammarstrom or Wadstrom and Robertson or WO, there is a reasonable expectation of success for one to include an elastase inhibitor in his new tissue adhesive.

Applicants respectfully submit that no *prima facie* case of obviousness has been properly established and thus request the withdrawal of the rejections under 35 USC §103.

CONCLUSION

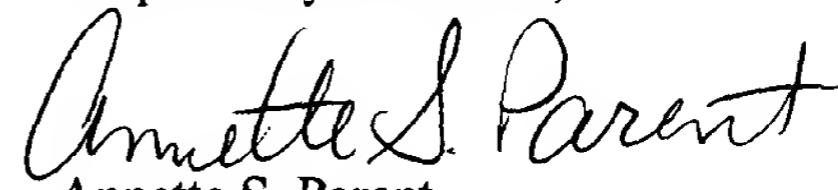
In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

REDL *et al.*
Application No.: 09/486,516
Page 8

PATENT

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (415) 576-0200.

Respectfully submitted,


Annette S. Parent
Reg. No. 42,058

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: 415-576-0200
Fax: (415) 576-0300
ASP:cg
SF 1371223 v1



REDL *et al.*
Application No.: 09/486,516
Page 9

PATENT

APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

On page 1, line 2, please insert the following headings and paragraphs:

CROSS REFERENCES TO RELATED APPLICATIONS

The present application claims priority to PCT/AT98/00202, filed August 26, 1998 and Austrian application number A 1449/97, filed August 28, 1997, herein incorporated by reference in their entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

Not applicable.

REFERENCE TO A MICROFICHE APPENDIX

Not applicable.

BACKGROUND OF THE INVENTION

On page 5, line 19, please insert the following heading:

SUMMARY OF THE INVENTION

On page 16, line 22, please insert the following heading:

BRIEF DESCRIPTION OF THE DRAWINGS

On page 17, line 15, please insert the following heading:

DETAILED DESCRIPTION OF THE INVENTION

IN THE ABSTRACT:

On page 19, please insert the following heading and paragraph:

ABSTRACT OF THE DISCLOSURE

The present invention provides a fibrinogen-based tissue adhesive which contains an elastase inhibitor.

IN THE CLAIMS:

29. (once amended) A tissue adhesive comprising [based on] fibrinogen[, said tissue adhesive comprising] and an admixed elastase inhibitor.

36. (once amended) A tissue adhesive as set forth in claim 29, wherein the ratio in weight of said elastase inhibitor to said fibrinogen is from 1:100 to 1:150,000 [said elastase inhibitor is contained in an amount ratio of from 1:100 to 1:150,000, based on milligrams of fibrinogen].

37. (once amended) A tissue adhesive as set forth in claim 29, wherein the ratio in weight of said elastase inhibitor to said fibrinogen is [the amount of said elastase inhibitor to fibrogen in a ratio] from 1:500 to 1:110,000.